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Cutting the Loops of Depression: a System Dynamics Representation of the Feedback Mechanisms Involved in Depression Development And Its Treatments

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Abstract

Depression is a complex illness that involves the instability of biological and psychological structures in an individual. These disturbances make a depressed person to be affected in the personal relationships within his social circles and to be unable to fulfill normal daily activities as expected. Once depressed individuals recognize the need for help, they might be part of 'therapeutic essays' based on doctors' experience and contemporary advances. These trial and error treatments can lead to unintended consequences that could worsen depression symptoms. Therefore, personalized treatments (a currently buzz term in the medical domain) are needed to reduce the time that an individual remains in a depressed condition. This paper contributes to treatment personalization of depression by presenting the first comprehensive feedback oriented model of the cognitive and biological structures involved in depression and how different treatments may bring the main affected indicators during depression back to their desired values. Moreover, the model generated with this project may serve as a tool for improving academic discussion around depression and also as a communication device for specialists (psychologists and physicians) to better communicate patients about their condition and how treatments may affect it.

Introduction

Depression is a complex illness that involves the instability of biological and psychological structures in an individual (Wittenborn et al 2015). These disturbances make a depressed person to be affected in the personal relationships within his social circles (family, school, work, etc.) and to be unable to fulfill normal daily activities. It is estimated that depression generates 400 million disability days for people aged 15-44 years in the United States, which is a general pattern in the rest of countries (Greenberg et al. 2010). Data is not precisely encouraging, taking into consideration that estimations from the World Health Organization (2011) indicate that depression will pass from being the third cause of disease burden to be the leading one in 2030. The forecast is worrying knowing that currently just 50% of patients go back to their optimal levels with psychotherapy (Barber et al. 2012) and pharmacotherapy has not yet demonstrated consistent advantages over placebo methods (Kirsch et al. 2008). These antidepressant medicaments are often prescribed under ‘therapeutic essays’ based on doctors experience and contemporary advances: a sort of *trial and error* method that tries to find the right pill that adapts to patient’s necessities, precisely the opposite way to what it would be thought. Since trial and error treatments may lead to unintended consequences that worsen depression symptoms, personalized treatments (a currently buzz term in the medical domain) are needed and recommended by researchers (e.g., Simons & Perlis, 2010) and could lead to reduce the time that an individual remains in a depressed condition and consequently decrease the millions spent in direct depression care, about 46% of the total costs of the illness (Greenberg et al. 2015). Now, in order to reach a personalized treatment approach, research should change the focus and pass from analyzing depression as a consequence of one variable to an interrelation dynamic system of psychological, biological and social structures (Wittenborn et al. 2015). Until now, research has been done primary in the opposite way and trying to find the one “essence” responsible for this mental disorder has covered 93% of all studies on this field versus the 7% of a multivariable focus (Wittenborn et al. 2015). The necessity of this shift in research has been recommended by researchers (e.g. Borsboom & Cramer, 2013) and more studies following this pattern, especially dynamic modeling for mental disorders, have been published in the last years (e.g. Wheat & Hassan, 2008; Susta & Bizik, 2011; Wittenborn et al. 2015). However, there has not been a comprehensive study of depression, looking at it in an aggregate level through the feedback mechanisms of cognitive and biological structures integrating not only the reinforcing feedback processes of depression, for instance done by Wittenborn and others (2015), but also the balancing feedback mechanisms that control depression development. Precisely, that is our contribution

with this project: extend prior attempts to understand the causal feedback mechanisms that underlie depression by generating the first dynamic comprehensive model of depression development in which the mechanisms by which different treatments options may affect the development of the disease.

System dynamics approach

As mentioned before, research and validation of depression has been done by separate parts of the whole picture. Therefore, we believe that more comprehensive studies that put all these pieces together are needed to develop a systemic view of depression, in order to examine how well contemporary discoveries, if they are put together, explain the development of depression. One tool that can add huge value for understanding the complex feedback mechanisms that underlie depression and in general mental disorders is System Dynamics (SD) modeling. This modeling technique helps to understand how the relationships among variables generate the formation of causal feedback loops that explain the behavior of a particular system (Vennix, 1996). From a system dynamics view, we believe that depression can be explained as the ‘battle’ for dominance between reinforcement of vicious cycles that worsens the disorder, reinforcement of virtuous cycles that generate positive affect and help fighting depression and balancing mechanisms that bring indicators through homeostatic processes to the normal levels. A reinforcing loop (virtuous or vicious cycle) describes how the impact of an increase in a variable, traced through a loop, leads to a further increase in that initial variable. For instance, in Figure 1, the increase of *perceived stress* due to an *exogenous variable*, for example, a relationship fight will generate *anxiety* to increase. Since the person is more anxious, *emotional stability* is decreased and also *depressive symptoms* start to rise, which finally increases *perceived stress*. Contrary, a balancing loop stops the increase of a variable and acts as a self-correcting process. In Figure 1, as a result of the presence of *depressive symptoms*, the person responds incrementing the *perceived actions needed*, put those *response actions* in practice, and decreases *perceived stress*.

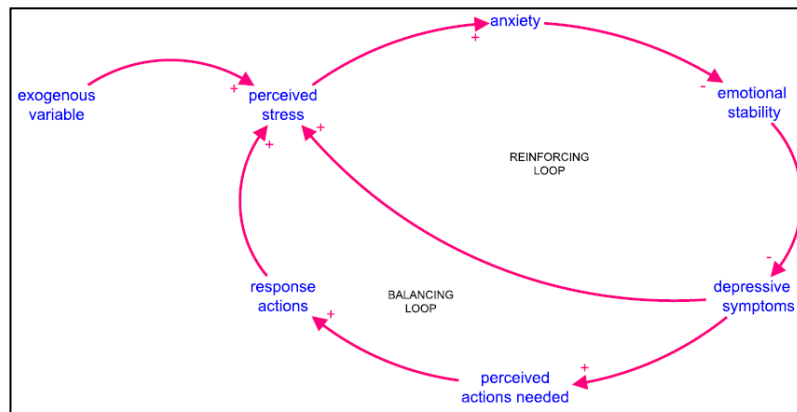


Figure 1. Representation of reinforcing and balancing loops from the concepts of a stress generation model from Morris and others (2010).

The interaction between the structures forming these two types of loops creates variability and oscillations (dynamics) within the indicators of a system, which in the case of depression we translate it as the changes in the individual's mood and behavior. Causal loop diagrams are useful for representing feedback processes within systems, however they lack to represent changes of variables over time such as rates or accumulation. In order to represent quantified models, System Dynamics uses Stock and Flow Diagrams (SFD). Four types of figures are identified in a SFD: stocks, flows, converters and links. Stocks are accumulations and they characterize the state of the system and give information for basing decisions and actions (Sterman, 2000). They are represented by a rectangle. Regarding depression, stocks will be variables which physicians would want to track at any specific time, for instance, hours of sleep, specific hormones (cortisol) or proteins levels. Flows are pipes that feed and drain those stocks over time. Figure 2 is an example of a Stock and Flow Diagram. There, the *cortisol level* stock is fed by a flow (inflow) called *increase in cortisol* and drain by a flow (outflow) called *decrease in cortisol*. Those flows are affected either in a positive or negative way by other variables called converters which are symbolized with circles. Connections are represented by links. The arrow of the link indicates the causal relation direction. For instance, a converter called *perceived stress* affects the increase of cortisol inflow and *physical activity* affects the outflow. The example is shown in.

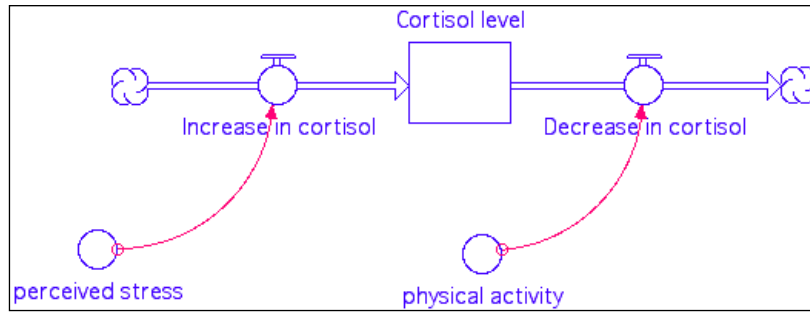


Figure 2. Stock and Flow notation example.

Our intention with the present project is to use System Dynamics as a communication device that could be used by professionals to better explain the mechanism underlying depression and the actions to take regarding treatments. We believe that building a comprehensive causal loop model that could include the different reinforcing and balancing mechanisms regarding depression is the first step towards the representation of depression dynamics into a Stock and Flow Diagram, which could be the next contributions.

Related applications

System Dynamics has had its main application in the social sciences domain since its creation in the second half of the 1950s (Vennix, 1996). The tool initially conceptualized for analyzing managerial problems from the viewpoint of information feedback control systems, has increased its application domains and for instance various problems in the health sector have been approached: disease epidemiology (cardiovascular, diabetes, obesity, cervical cancer, Chlamydia, dengue fever), substance abuse epidemiology (cocaine, heroin, tobacco) and health care management related issues (Milstein & Homer, 2009). The application of system dynamics within mental disorders is not broad, however studies have confirmed the usefulness of modeling both to better understand specific problems and to communicate audiences and achieve consensus about results and future research (e.g., Wittenborn et al. 2015; Wheat & Hassan, 2008; Susta & Bizik, 2011). The most complex system dynamics qualitative model to understand depression development has been recently published (December 2015) by Wittenborn and other (2015). In this model, the authors included the current validated psychological, biological and social relationships. The study portrays thirteen reinforcing loops presented under three dimensions: cognitive, social and environmental, and biological, which would partially explain depression development from an endogenous point of view.

According to the authors, the endogenous perspective explains how after a stressful situation and a “shock to the individual’s system” (affecting the equilibrium in which a person remains), depression reinforcing loops would carry some individuals to worsen “depression indicators” under three levels: increase in negative cognitive representations, increase disturbances in hormonal levels, and decrease in social, economic and health resources (Wittenborn et al. 2015). Even though the structure of this qualitative model was validated by experts during its execution, the development of quantitative models that help validating the output of the model is necessary and acknowledged by its authors. These types of quantitative models will have a lower scope due to the difficulty of having all concepts together in one model taking into account that current discoveries still lack from “total” consensus (Wittenborn et al. 2015). Precisely, some authors have worked in that direction, reducing the scope of their work to focus with more detail in certain feedback loops involved in biological factors of depression, specifically generating formal system dynamics models that explain the behavior over time of some of the hormones participating in depression: cortisol, corticotrophin releasing hormone (CLH) and adrenocorticotrophin (Hosseinichimeh et al. 2015). This type of approach, quantitative model, generates a great impact to prove current assumptions and a better understanding of the dynamics over time of a specific event or phenomenon (Homer & Oliva, 2001). Ultimately, these models seek to generate impact in people involved in depression treatment implementation, namely doctors and patients, in order to aware them of all the structures (variables) playing a role and intervening in depression. Now, taking the current research into depression causality models, our intention is to go one step before and generate the first comprehensive causal loop model of depression development which includes the main reinforcing and balancing feedback processes. This model could then serve as a base to generate quantitative models regarding depression dynamics and compare the simulation results with real patients data.

Relevance and contribution

As mentioned before, there has not been a broad comprehensive feedback oriented study of the cognitive and biological structures of depression, other than the work of Wittenborn and others (2015) who focus on the reinforcing mechanisms of depression, missing, as they recognize, the balancing mechanisms that stop or control depression, and let patients recover. In that way, this project is a contribution to the academic community as a systemic analysis of depression that could translate the current knowledge of depression in a dynamic simulation model, showing how depression can be explained through reinforcing and balancing feedback

mechanisms of cognitive and biological variables, and how different treatments (specifically cognitive therapy, pharmacotherapy, meditation and physical exercise) may affect the development over time of this mental disorder. Moreover, the model generated with this project is intended to be used by physicians and psychologists to better communicate patients about the development of depression and how treatments can approach it; considering that currently just one-half of patients initiating antidepressant treatment return for follow-up visits (Simons & Perlis, 2010). In order to perform this, we will review and translate the contemporary literature into causal feedback mechanisms to generate a broad causal loop diagram, always considering that the terminology must remain without medical or scientific wording to be more accessible to patients as well.

Research objective and questions

In order to achieve a dynamic model that explicitly integrates the current knowledge of depression development, the project's research objective is to design a comprehensive causal loop diagram that shows the interactions between the main reinforcing loops that worsen the illness and the balancing loops that control its development. The model has a double intention. First, it is intended to be a learning tool, for the academic community, that represents in a qualitative model the interactions between different structures of depression (cognitive and biological measures) and the unintended consequences of wrong approaches and treatments, therefore being the base for future quantitative approaches. Second, it is expected to be a communication tool that specialist (physicians and psychologists) could use to explain their patients about this condition and the mechanisms behind the different treatments. In that way the model translates scientific (cognitive and biological) terms into common terminology in order to be accessible to commoners. In the end, the project intends to aware stakeholders of the necessity to measure indicators through treatment since those indicators will be the drivers to see the results start, modify or stop specific treatments. The research questions that leverage the fulfillment of the mentioned objective are:

- What are the feedback-processes resulting from the interaction of cognitive and biological structures during depression?
- How can different treatments affect the dynamics of the desired levels from cognitive and biological structures?

Methods

In order to achieve the first comprehensive model of depression dynamics and its treatments, our strategy to organize the comprehensive causal loop diagram was based on the work of Wittenborn and others (2015). The CLD presented in that publication is the first extensive explanatory approach of the reinforcing loops involved in depression from a system dynamics view. We considered that the broad model boundary used in that work, including a cognitive, social and biological dimension, was an adequate approach for our work. In our case we decided to merge the cognitive dimension with the social and environmental, since in our understanding, the abstraction (perception) of the social dimension can be understood as cognition. Thus, two dimensions were chosen (cognitive and biological) for mapping the reinforcing and balancing mechanisms of depression. Besides, we planned a specific section for the analysis of four specific treatment options (cognitive behavioral therapy, pharmacotherapy, mindfulness meditation and physical exercise).

Problem definition

Once the organization of the literature review was selected, we proceeded to process the data. The theories and concepts were selected from review papers, and the starting point was the list of references used to construct the model from Wittenborn and others (2015). We then used the referenced articles from those papers but also the most referenced and used generic theories of depression. This process was executed first for the cognitive dimension and later for the biological one, and every major concept was translated into small causal loop diagrams in order to clarify and visualize the relationship of every structure and to ease the future model building process. An important aspect that was analyzed during the literature review was the level of detail of the selected concepts. We chose an aggregate level to represent the concepts regarding depression. For instance, when the neurotransmitters group was approached within the biological dimension, not every type of neurotransmitter was considered but the causal relationship of the entire group with other structures. The variables' names were also an important aspect to consider during the representation of concepts into causal loop diagrams. Since our intention was to produce a qualitative model that could ease the communication between specialists and patients, the terminology used in the diagrams was neither academic nor scientific, unless strictly necessary. For example, within the biological dimension, the most difficult section to follow, we used generic biological terms and for example, cytokines were named either pro or anti-inflammatory proteins, and

glucocorticoids were named circulating hormones. We chose this approach since we believe that scientific terms might confuse audiences and generate distance to the model.

System conceptualization

After introducing and diagramming each individual concept, the next step was to put them together into broad comprehensive causal loop diagrams. In order to represent the diagrams, an iterative process of organizing and editing was used, and the concepts of some theories were merged and consolidated in aggregate terms. For example, within the cognitive dimension, the terms self-perception of social acceptance and self-perception of scholastic competence, both from the Competence Based Model, and the terms self-perception of security, acceptance and respect, and self-perceived autonomy, both from the Maladaptive Schemas Theory, were combined into a single concept called self-perception. A similar process was used for other structures. Besides showing the direction of every causal relationship, the formed loops were named and then explained by unfolding the model. Two broad causal loop diagrams were the result of the analysis. In the first diagram, the biological and cognitional structures influencing depression dynamics were included. There, depression is explained as a result of the interaction between different feedback mechanisms once an external shock affects the individual's equilibrium. Now, in order to portray the second causal loop diagram, the one including the mechanisms behind the four chosen approaches (pharmacotherapy, psychotherapy, meditation and physical exercise) were first explained individually. Later, they were presented in the final product of this research study, generating the first comprehensive causal loop diagram of depression to understand how the disease is a result of different endogenous feedback processes and how different treatments may affect its behavior over time.

Results.

Within the literature review (see appendix A), the main psychosocial and biological theories and concepts regarding depression were individually represented and translated into causal loop diagrams in order to visualize the direction of every effect (positive or negative), understand the feedback mechanisms and ease the building process. In this section, the mentioned concepts are put together in order to achieve a final and consolidated comprehensive causal loop model. Since the causal loop diagram is intended to be a communicational tool that could serve specialists to communicate patients, the terms remain simplistic and academic or medical terms are restricted unless strictly necessary. Two broad

causal loop diagrams were generated. First, the biological and psychosocial structures influencing depression were included in one diagram. The second CLD includes the variables regarding treatments to visualize how they try to approach depression.

Translation of depression development over time

In our understanding from the literature review, there are four specific concepts that should be represented in a comprehensive causal loop diagram as a translation of the cognitive dimension of depression. The concepts are: perceived stress, self-perception, interpersonal problems and overthinking. On the basis of the literature review, we believe that the four concepts listed above can be understood as the foundation for the cognitive and social processes regarding depression development over time. Now, regarding the biological structures involved in depression, in our understanding the most important ones, in an aggregate level, are certainly: anti-inflammatory and pro-inflammatory proteins, circulating hormones and neurotransmitters activity.

In order to represent how depression develops in a causal loop diagram, both the normal functioning of cognitive and biological factors, together with their impairments must be included to represent the interactions between reinforcing and balancing loops. As an iterative process of putting together the concepts presented in the literature review, we develop the comprehensive CLD shown in Figure 3. This diagram represents, from an endogenous point of view, the different feedback processes that would drive depression.

In the following section we explain how the different loops presented in Figure 3 would be activated to create the dynamics in depression development.

Explaining the model.

We will assume that the *initial external stress shock* presented in Figure 3 comes from a specific interpersonal relationship problem with a close person (partner, familiar, friend). Thus the initial affected variable is *interpersonal relationships quality*. The *initial external stress shock* has a double effect. On one side, the person responds to the decrease in *interpersonal relationships quality* adding more pressure to expand his (her) *individual solving capacity*, in order to be able to solve the inconvenient. This increase in the *individual solving capacity* allows an increase in the *ability to increase interpersonal relationships quality*, and the person recovers the previous *interpersonal relationships quality* or is brought back to an accepted level. We have named this controlling mechanism (loopB1) as the “flexibility for solving interpersonal problems”. Now, if a person does not solve the diminishment in *interpersonal relationships quality* in an adequate manner, the person starts to increment the levels of *perceived stress*. The increment in *perceived stress* will begin a chain of chemical processes in the body. First, *perceived stress* increases the production of *pro-inflammatory proteins*, which alert the brain to reach a *desired circulating hormones* level. If the *desired circulating hormones* are higher than the *current circulating hormones*, the brain starts the production of hormones until the gap (difference) between them is close. The loop B2 (hormones regulation through HPA axis) represents that controlling mechanism. This feedback loop brings the *current circulating hormones* to the *desired circulating hormones* level and it is the first step towards the stress response. However, if the individual has to deal with a *perceived stress* that is permanently high, there will be high levels of *pro-inflammatory proteins* and the *desired circulating hormones* will be consistently high as well. Since the brain is constantly sending the signal to produce a high quantity of *hormones*, there is a sort of burnout of the *hormones receptor quality*. The hormones receptors are the structures responsible for estimating how much circulating hormones are needed; thus the decrease in the *hormones receptors quality* means that the *desired circulating hormones* will not be “calculated” in an adequate manner and there will be a tendency to overestimate the desired amount. For example, during high levels of *perceived stress*, if the brain is “asking” for a 10% increase in the *desired circulating hormones*, the impaired *hormones receptor quality*, makes that a higher percentage is asked for, which is translated into a constant

overconcentration of *circulating hormones* in the blood and brain. The reinforcing loop R1 (“hormones receptor malfunction”) shows this feedback process.

Current circulating hormones have special importance during depression since they are precursors of *anti-inflammatory proteins*, which are the structures responsible for turning off inflammation. Thus, when there are more *current circulating hormones* in the blood, more *anti-inflammatory proteins* can be activated. The increase in *anti-inflammatory proteins* serves to decrease *pro-inflammatory proteins*. The loop B3 (Anti-inflammatory proteins regulation) represents that balancing mechanism. However, *current circulating hormones* are not completely beneficial within the body. When *current circulating hormones* are overconcentrated in the blood, they may access the brain and reduce the *effectiveness of anti-inflammatory proteins*. Thus, the “power” of *anti-inflammatory proteins* decreases and even when they are produced, they are not effective to decrease *pro-inflammatory proteins*. We have named this reinforcing feedback process (loop R2) as “chronic inflammation”.

The presence of chronic inflammation is prejudicial for depression, since the abundant *pro-inflammatory proteins* will synthesize (combine) with other biological structures within the brain, producing certain enzymes that increase the *neurotransmitters reuptake impairment*, which finally reduces *current neurotransmitters activity*. One key process affected by changes in *current neurotransmitters activity* is sleep (*average hours of sleep*). In aggregate terms, sleep has two important phases regarding inflammation. At the beginning of the sleep cycle *pro-inflammatory proteins* are generated and by the end of the cycle (almost when the person is waking up) *anti-inflammatory proteins* are generated. Therefore, when *current neurotransmitters activity* maintains a healthy level, *average hours of sleep* do not suffer any disturbance and the *anti-inflammatory proteins* produced during the last part of a healthy sleep cycle, can counteract the *pro-inflammatory proteins* produced at the beginning of the sleep cycle. The loop B4 (sleep regulation) represents that process. However, when *current neurotransmitters activity* drastically decreases, the person starts presenting malfunction in his (her) sleep patterns and the *average hours of sleep* (together with the quality) start decreasing. Thus, the *pro-inflammatory proteins* (generated at the beginning of the sleep cycle) are not depleted and start to be abundant in the brain, worsening the *neurotransmitters reuptake impairment* and decreasing *current neurotransmitters activity*. We have named this reinforcing process (loop R3) as “sleep incomplete anti-inflammation regulation” and it is activated when *average hours of sleep* are too low. Due to the increase in *neurotransmitters reuptake impairment*, *current neurotransmitters are reduced*, and consequently the *working memory* of an individual is reduced. Since the individual’s *working memory* does not work as

expected during depression, the person decreases the *ability to increase interpersonal relationships quality*. Thus, even when the person can use his (her) *individual solving capacity* to increase the quality of his relationships, he (she) is not able to do it, which brings more *perceived stress* to the individual, perpetuating depression. We have named this reinforcing feedback loop (R4) as “neurotransmitters reuptake impairment”. The loop B5 (ability to decrease negative interpretations) is the opposite of R4. When there is not *neurotransmitters reuptake impairment* (or the impairment is relatively low) the individual’s *current neurotransmitters activity* permits a healthy *working memory* and the individual has the *ability to increase interpersonal relationships quality* by decreasing any interpersonal problem.

Another consequence of neurotransmitters disturbances (in this case lower levels of *current neurotransmitters activity*) is the likelihood of increasing *overthinking time*. Individuals do not perceive instantaneously changes in *over thinking* time, but just when *overthinking time* starts to strongly interfere with normal daily thinking processes. As a response to the increase in *overthinking time*, people increase their *willingness to engage in pleasant activities* in order to increase their *distraction time*. *Distraction time* is translated into the body as *anti-inflammatory proteins*, which reduce the inflammation (caused by *pro-inflammatory proteins*) that *perceived stress* produces. The loop B6 (distraction and positive affect generation) represents this balancing mechanism. Nevertheless, high levels of *over thinking time* may start a dangerous reinforcing loop for depression. Generally, *overthinking time* drives more *accessibility to negative events* (thoughts) in each individual’s mind, and with the time the person starts increasing his (her) *responsiveness to thoughts*. With high levels of responsiveness the individual feels that he (she) has to fight and eliminate every negative thought from his (her) mind. Since thoughts may arise at any moment the person feels trapped in his (her) own mind and perceives that engaging in pleasant activities does not help to distract from the stress sources. Therefore, the increase in *responsiveness to thoughts* starts diminishing the *willingness to engage in pleasant activities*, and consequently the levels of *distraction time* are lower, and less anti-inflammatory proteins are obtained. We have named this reinforcing feedback process (loop R5) as “fighting thoughts reaction”.

Another effect of increasing the *accessibility to negative events* is the depletion of *working memory*. When a person presents lower levels of *working memory*, his (her) *cognitive performance* is diminished, and the person is less able to process and memorize important information for his (her) normal daily activities. Due to the decreased *cognitive performance*, problems start to accumulate over time, leading for instance to layoffs or resignations at work.

As a result, the *self-perception* of the individual about himself (herself) starts to be depleted over time. On one side, individuals use this diminishment in their *self-perception* as a motivation to improve in certain valuable characteristics (for example economic security, social acceptance or emotional support). Thus, people create a *perceived goal for personal valuable characteristics* as a comparison between their *self-perception* and the *perception of valuable characteristics of significant others*. Based on that perceived goal, the necessary *corrective actions for desired perception* are taken over time, which brings *self-perception* to desired levels. That process is represented in loop B7 (“coping strategies for desired personal characteristics”). Now, when time has passed and the person is not able to achieve the *perceived goal for personal valuable characteristics*, the person experiences *frustration for the inability to obtain valuable characteristics*, which increases the levels of *perceived stress*, generating another reinforcing loop (R6), “frustration for non obtained goals”.

As a result of the recurrent erosion of *self-perception*, the *perception of valuable characteristics of significant others* will seem to be more important with the time, therefore the *perceived goal for personal valuable characteristics* is becoming bigger and bigger. This brings more urgency for improvements, and the persons takes more *corrective actions for desired perception*, but when results are not obtained, it specially increases the *frustration for the inability to obtain valuable characteristics*, generating higher levels of *perceived stress*. Therefore, there is an “overestimation of other’s personal and social characteristics” which is the name of the reinforcing feedback loop R7. Finally, as a result of the diminishment in *self-perception*, the person starts isolating from his (her) social circles, diminishing the amount of time or the quality of encounters, provoking lower levels of *interpersonal relationships quality* and bringing depression symptoms to deeper levels. The loop R8 (cognitive deficit) represents that process.

Translation of depression treatments

In the previous section we explained how based on an external stress shock, the interaction between reinforcing and balancing loops, which are generated from the relationships between biological and cognitive structures, would contribute to the development of depression over time. We consider that the previous causal loop diagram (Figure 3) could help explaining why individuals present depressive symptoms but it does not communicate how the different treatments options can be effective tools to counteract depression. Our objective within this section is to include the mechanisms behind the four different treatment approaches discussed in the literature review as an extension of Figure 3.

Based on the literature, we have identified four crucial indicators regarding depression, which would represent the “performance drivers” that could initiate, modify or stop a specific treatment. Those structures (variables within the causal loop diagram) are:

- Current neurotransmitters activity
- Current circulating hormones
- Responsiveness to thoughts
- Self-perception

Each treatment will seek to affect one of those variables by bringing them to desired states. For example, by engaging in meditation the current level of responsiveness to thoughts could decrease until the person develops an observational attitude to his (her) thoughts, starting a chain of positive effects. This mechanism, as well as the ones by which the rest of treatments would improve depression symptoms, but also the unintended effects of every approach will be individually explained. As a last step the four approaches considered will be shown in a comprehensive causal loop diagram.

Physical activity

The introduction of physical activity as a treatment approach for controlling the level of circulating hormones could be an effective complementary option for reducing depressive symptoms. As we explained in the causal loop diagram of depression development (Figure 3), high levels of circulating hormones could be counterproductive for the individual as they may activate dangerous mechanisms (reduction of the effectiveness of anti-inflammatory proteins, reduction of the hormones receptor quality), which will start a chain of prejudicial processes due to the interconnection of the rest of biological and cognitional structures. In Figure 4, we show how physical activity may reduce depressive symptoms through the diminishment of hormones overconcentration. Physical activity as a mechanism for depression would start with the detection of the level of *current circulating hormones*. The *gap for desired circulating hormones*, originated from the comparison between the *desired daily circulating hormones* and the *current circulating hormones* would start the *physical activity* approach. Now, it is especially important to adapt physical activity to the characteristics of the person determining an adequate frequency and time in order to reach the goal: decrease current circulating hormones. If current circulating hormones are daily decreased, the *hormones receptors quality* is not diminished and the effect of hormones overconcentration in anti-inflammatory proteins effectiveness does not appear. That is shown by loop B8 (hormones overconcentration avoidance). However, if exercise (physical activity) is exaggerated and the

individual exercises with a high intensity (60% or higher); the current circulating hormones will increase, starting a chain of negative processes (worse depressive symptoms) through the diminishment of both hormones receptor quality and effectiveness of anti-inflammatory proteins. The feedback process (R9) “production of hormones for over-exercising”

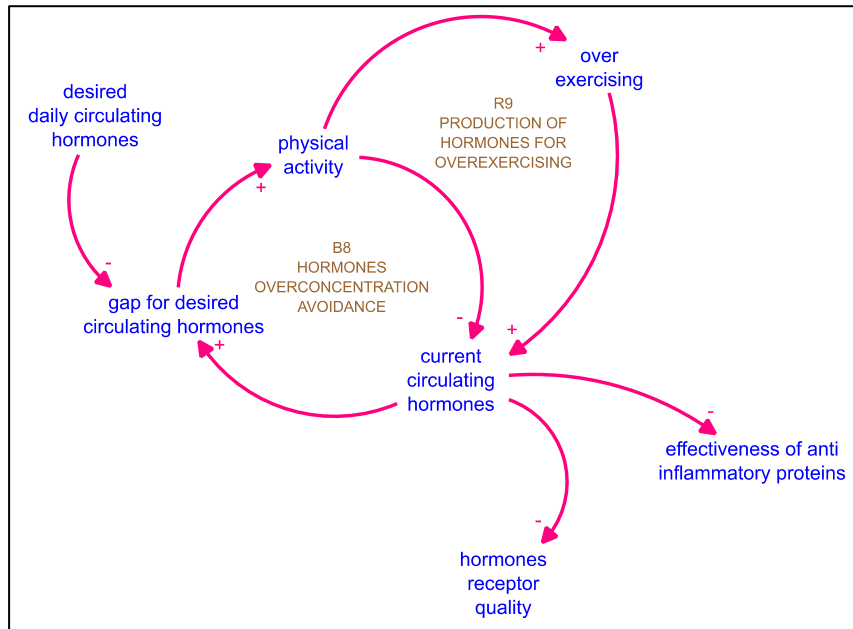


Figure 4. Physical activity as a mechanism to reduce hormones overconcentration in depressed individuals

Antidepressants pharmacotherapy

The hypothesis behind the initiation of pharmacotherapy is that problems are caused because of the reduction in *current neurotransmitters activity*. Therefore, the goal with antidepressants, using system dynamics terminology (Figure 5), is to react on the *gap for desired neurotransmitters activity*, which is originated from the comparison between the *current neurotransmitters activity* and the *desired neurotransmitters activity*. The gap will induce the start of *antidepressants pharmacotherapy*, which after a delay will start increasing *neurotransmitters activity*. The loop B9 (balance of neurotransmitters activity) represents that feedback process. Due to the increase in *neurotransmitters activity*, the person improves his (her) *average hours of sleep*, starts to decrease *overthinking time* and reduce the *accessibility to negative events*. This generates an increase in *working memory* and it is finally translated into a better *cognitive performance*, boosting the individual's *self-perception*. However, antidepressant pharmacotherapy brings side effects that could affect the levels of depression. Especially important is the positive relationships between *antidepressant pharmacotherapy* and *sleepiness and dizziness sensation*. Due to the increase of *sleepiness and dizziness*

sensation, the person decreases his (her) *cognitive performance*, meaning that the individual is less productive for daily activities, finally affecting negatively his *self-perception* (the person starts making inferences about his poor performance). With the diminishment of *self-perception*, the person may fall in deeper levels of depression due to the activation of various reinforcing loops (through interpersonal relationships quality, perceived stress, pro-inflammatory proteins, among others). The loop R10 (pills side effects) is a representation of that.

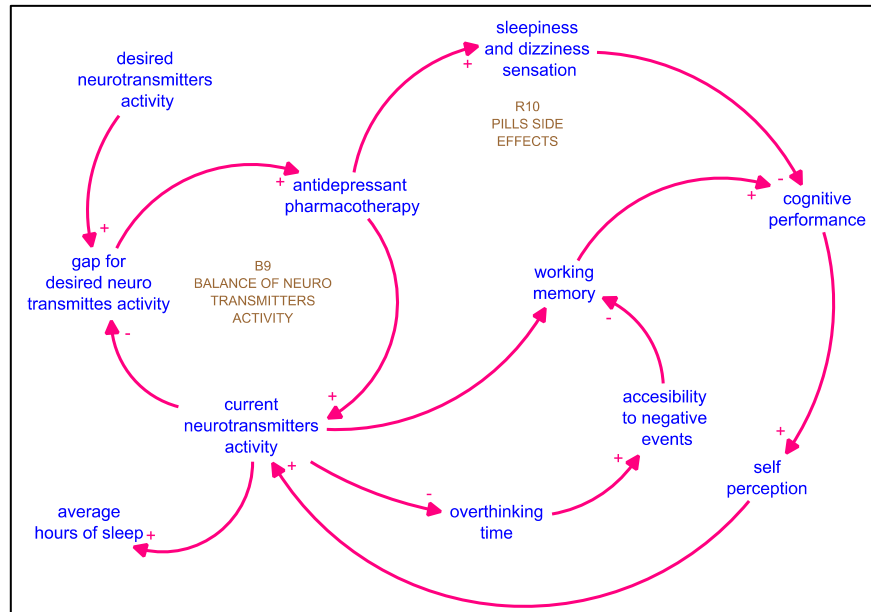


Figure 5. Pharmacotherapy as a mechanism to increase neurotransmitters activity in depressed individuals.

Mindfulness meditation

The objective of mindfulness meditation (meditation in general) is to disengage from self-perpetuating patterns of negative thoughts by changing the relationships with them, that is, re-perceiving them. Considering that, in Figure 6 we show how mindfulness meditation would bring benefits to depression. With mindfulness meditation the goal, using system dynamics terminology, is to react on the *gap for responsiveness to thoughts*, which is originated from the comparison between the individual's current *responsiveness to thoughts* and the *desired responsiveness to thoughts*. The existence of the gap will induce the *mindfulness meditation practice*, which if maintained through time, will reduce the *responsiveness to thoughts*. We have named this balancing loop (B10) as "reduction of responsiveness through meditation". If achieved successfully, the decrease in the *responsiveness to thoughts* lets the individual to increase the *willingness to engage in pleasant activities* (thoughts interfere less in the

individual willingness). As a result, the person increases *distraction time*, producing more *anti-inflammatory proteins*, which will drive a series of positive processes both biological and cognitional. It is important to mention that while mindfulness meditation may reduce the *accessibility to negative events* (through the loop B6, distraction and positive affect generation). The person will still access negative events in his (her) mind, but since the responsiveness to thoughts is better managed, relapses may be reduced.

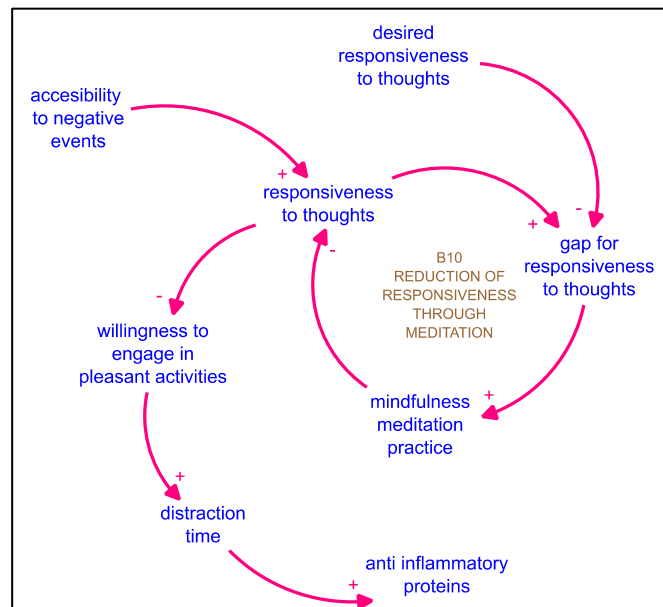


Figure 6. Mindfulness meditation as a mechanism to decrease responsiveness to thoughts

Cognitive behavioral therapy

The introduction of cognitive behavioral therapy in depressed individuals may share some relieving mechanisms with mindfulness meditation. For instance, the impact of negative thoughts is intended to change. While meditation attempts to learn how to let thoughts come and go, cognitive behavioral therapy attempts to change the negative interpretation of those thoughts and change behavioral patterns that arise from them. Thus, in our perspective, in aggregate terms, improvements in *willingness to engage in pleasant activities* may be accomplished by both approaches. For this reason, we limit to use cognitive behavioral therapy as a mechanism to improve self-perception. In Figure 7 we present how those will work. *CBT sessions* will start as a result of a considerable gap for desired self-perception, which is generated from the difference between the individual self-perception and a desired self-perception. Now, with the increase in *CBT session*, more *identification of negative patterns* can be achieved and, as a result of different psychological exercises, the person may reduce the *perception of valuable characteristics of significant others*. Since the person stops

overestimating the characteristics of others, the *perceived goal for personal valuable characteristics* decreases and the *corrective actions for desired perception* are easier to achieve, finally boosting self-perception. The loop B11 (“no perfection in significant others”) represents this concept. Besides, the *identification of negative patterns* lets the person decrease the *frustration for the inability to obtain valuable characteristics*, since he (she) is taught to be less responsive to those thoughts. Therefore, the person generates lower levels. The link between *perceived stress* and *self-perception* is a shortcut for various mechanisms involved (for example pro-inflammatory proteins, current neurotransmitters activity, overthinking among others). The loop B12, named “acceptance of no deadlines” represents this process.

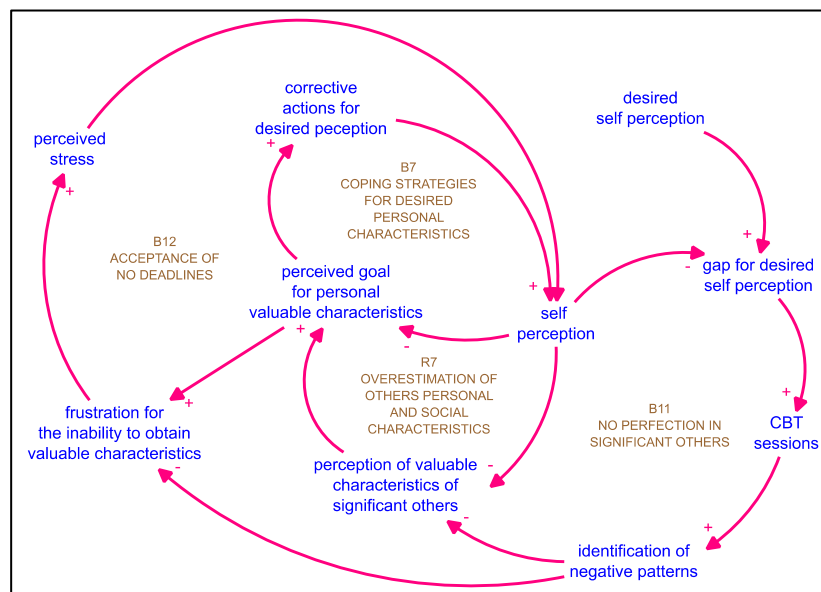


Figure 7. Cognitive behavioral therapy as a mechanism to increase self-perception in depressed individuals

Final comprehensive model of depression development and treatment approaches.

Once we have explained individually the mechanisms by which the four treatment options may bring the levels of neurotransmitters activity, circulating hormones, responsiveness to thoughts and self-perception, to their desired states, we present them in a comprehensive causal loop diagram in Figure 8. As it was the purpose of this project the diagram is a result of the translation of the contemporary knowledge about depression in the first comprehensive model of depression development. Also, as it was our objective the model is generated in common language (avoiding as much as possible scientific terms) in order to have a tool that could be accessible to patients to understand their condition.

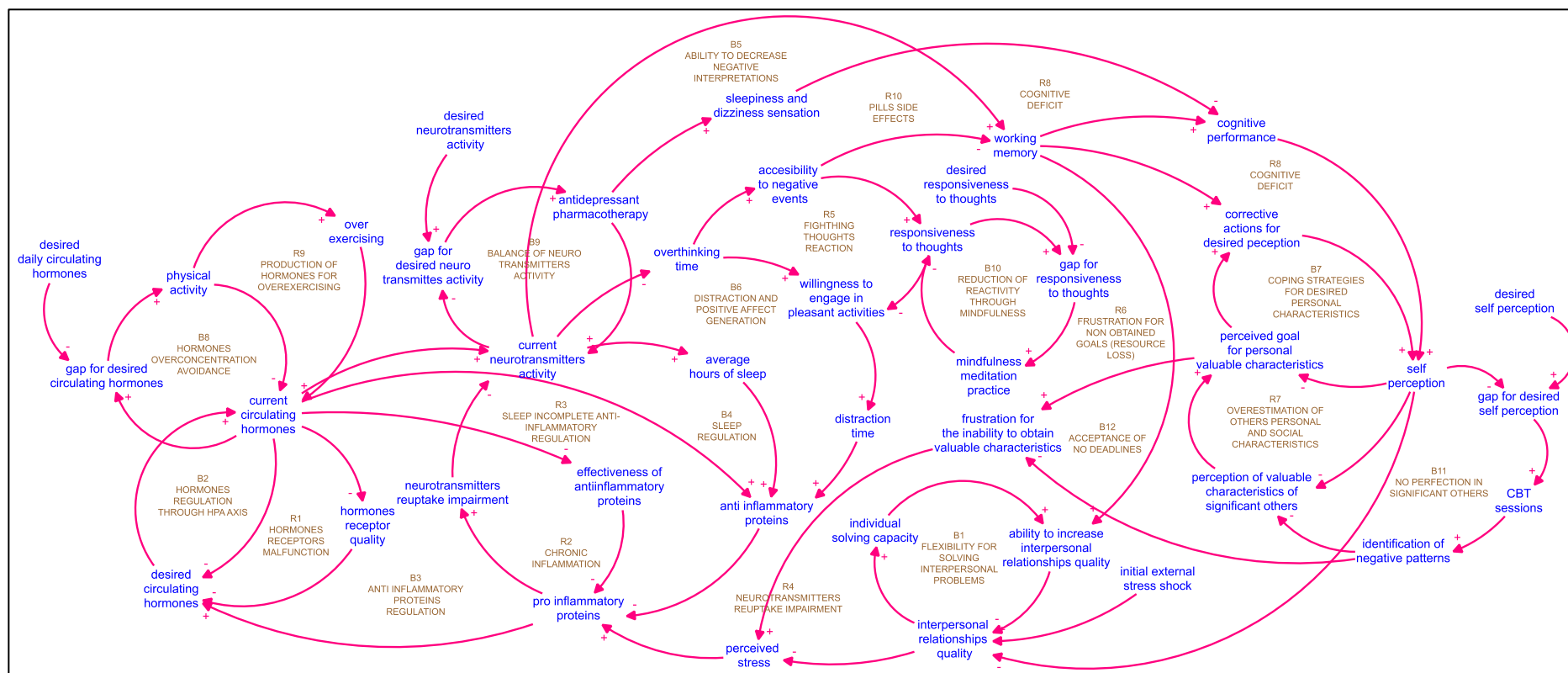


Figure 8. Comprehensive causal loop diagram of depression development and treatment approaches

Discussion

The model presented in Figure 8 is the first comprehensive qualitative model about the mechanisms behind depression development, and its treatments approaches. The model uses a causal loop diagram to identify the main feedback processes involved in depression, formed by the interaction of cognitional and biological structures, and explain how after the appearance of an external stressor, the interaction between those feedback processes may drive some individuals to depression. There are five specific insights that we stand out from the final model of this project.

- *Depression as an endogenous process.* The consideration of depression as an endogenous process, resulting from the interaction of different cognitive and biological structures serves as a proof of why different treatments might get similar results. For example, when approaching depression in different manners, for instance, pharmacotherapy and psychotherapy, the two of them preset successful cases, which confirm the idea of depression being an group of interrelated structures.
- *The usefulness of personalized treatments.* Specialists could offer personalized treatments to depressed individuals based on the identification and measurement of specific “indicators”. Thus, they might use a combination of different approaches (we considered pharmacotherapy, psychotherapy, meditation and physical activity) to bring the levels of specific indicators back to their desired values. While working on neurotransmitters activity, circulating hormones, responsiveness to thoughts and self-perception, the individual would be able to decrease the strength of specific damaging loops and decrease depressive symptoms.
- *Decrease the likelihood of relapses.* Combining different approaches might be beneficial to avoid depression relapses in individuals. Even when some persons might stop or reduce depressive symptoms just with one approach, for instance, pharmacotherapy (antidepressant pills) or physical exercise, the presence of psycho education (cognitive behavioral therapy and meditation) is crucial to reduce the likelihood of depression relapses, since it teaches the person how to deal with stress, reducing the biological effects of it. Thus, in the short-term antidepressants or physical exercise might serve to deactivate the dangerous loops of depression but in the long-run there is a necessity to change cognition. Once the responsiveness to stressors is diminished, physical activity might serve as sort of replacement of antidepressant pills when hormones or pro-inflammatory proteins start to escalate.

- *The model as a communication tool.* We believe that the model presented in Figure 8 can serve specialists to communicate patients about their condition and why treatments are considered. Currently, when specialists tell patients about depression they usually refer to it as a result of a chemical imbalance, a genetic disorder or the presence of environmental stressors. Now, considering that the concepts of virtuous and vicious cycles are frequently used by commoners, we assume that introducing a causal loop based explanation of depression might help the patient to understand why a specific treatment will be taken and how it would affect his condition.

Limitations and future research

Currently, the scientific knowledge about depression, and in general mental disorders, is still far from being complete. In the mental disorders contemporary literature various contradictions can be found and there are still several mechanisms stated as hypothesis. Therefore we acknowledge that our model may mimic those similar “mistakes” and could be perfectible with future contributions. To cite an example, we chose pro-inflammatory proteins as precursors of circulating hormones even when in some studies the opposite is stated. We also comprehend that our model is sizeable (41 variables and 23 feedback loops) and could be difficult to translate into a quantified version without first taking small steps towards that and simulating sections of it. However we still believe that for communicational purposes it keeps a good balance and could be a powerful tool regarding academic discussion and communication to depressed individuals.

We should mention that due to the extension of the model we did not include the “frustration for poor results” mechanism that all treatments share. Since most treatments regarding depression take time to create positive effects, especially the psychological ones due to the required change of mindset, this mechanism will appear once the individual feels that the “indicators” of depression are not changing. This motivation erosion could make the depressed individual leave any treatment and perpetuate depression. The personalized treatment approach should include support to avoid frustration to appear, constantly reminding the individual of the goal of each treatment. Models regarding goals erosion are a good source to understand this process and future work could use those structures to include in depression causal models. Finally, we comprehend that our model, being a qualitative one, is limited to fully understand the power of specific feedback processes and also lacks the capacity to compare which treatment options could be more effective in specific scenarios. We consider that future research is needed to develop quantitative simulation models of

depression treatments in order to get more insights regarding personalized treatments. Those models could predict how depression dynamics can change when adjusting the treatment to each individual. For instance, how the intensity and time for physical exercise, can decrease overconcentration of hormones and pro-inflammatory proteins, or how effective each treatment could be in comparison with a combination of them.

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APPENDIX A. LITERATURE REVIEW

Definition of mental disorders

Standardization of mental disorders diagnosis is a crucial aspect for ensuring consistency and avoiding vague illnesses descriptions among the mental health professionals community. For this reason, specialists use diagnosis coding for classifying medical conditions (Winfried & Mohan, 2007). Currently, there is not just one classification system and depending on the region different versions are used. However, the two most respectable institutions for defining and categorizing mental disorders are the World Health Organization (WHO) and the American Psychiatric Association (APA) (Winfried & Mohan, 2017). The Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) is used by the APA as the documenting instrument for categorizing mental disorders while the WHO uses the section F of the International Classification of Diseases (ICD) (Benazzi, 2006). In both manuals, mental disorders are defined as health conditions involving changes in thinking, emotion or behavior (or a combination of these) causing distress or problems in social, work or family activities (American Psychiatric Association, 2016; World Health Organization, 2015). Among all types of mental disorders, depression is the most common one, currently affecting more than 350 million persons worldwide, according to estimations (World Health Organization, 2015). Those changes in “thinking, emotion or behavior” presented in the definition are precisely, in our opinion, the oscillations generated by the interaction between reinforcing and balancing loops that this project seeks to represent.

Definition of depression

The APA characterizes depression (major depressive disorder) as a medical condition that negatively affects the way a person feels, thinks and acts. In general, it is established that depression causes mainly “feelings of sadness or loss of interest in activities once enjoyed” (World Health Organization, 2015). However, plenty of other symptoms have been recognized:

- Sleeping disorders (insomnia or hypersomnia)
- Eating disorders (decreased or increased)
- Loss of energy
- Psychomotor agitation or retardation
- Feelings of worthless and guilt
- Diminished ability to think

- Diminished ability to concentrate
- Difficulty for making decisions
- Suicidality

According to the Diagnostic Statistical Manual for Mental Disorders (DSM-IV), the criteria for being diagnosed with depression are (Benazi, 2006):

- Five or more symptoms present during the same 2-week period, where at least one symptom must be depressed mood or loss of interest/pleasure.
- The symptoms must not meet criteria for a mixed episode.
- The symptoms must cause clinically significant distress or impairment of functioning.
- The symptoms must not be related to substances, medical disorders or bereavement (loss).

Types of depression

Within the medical community there are different opinions for categorizing depression (in general mental disorders) but essentially they could be divided into two type of “schools”: whether they should be represented as discrete categories of depression (categorical view) or as a continuous condition (dimensional view) (Haslam, 2003). The categorical view proposes different forms of depression, while the dimensional view contemplates just one same disorder, manic-depressive insanity, with different combinations (Haslam, 2003). Currently, the categorical view is used within the medical community and the typologies established by the World Health Organization (WHO) and the American Psychiatric Association (APA) are the ones employed. The WHO defines three severities of depressive episodes: mild, moderate and severe and differentiates between bipolar affective disorder and recurrent depressive disorder. A person with bipolar affective disorder experiences manic episodes (elevated or irritable mood, great excitement or euphoria) together with depressive episodes, separated by normal mood periods; while a person with recurrent depressive disorder will repeatedly experience the symptoms of depression without presence of mania (World Health Organization, 2015). On the other side, the dimensional view of depression establishes that there are not different kinds of depression but rather different intensities. Thus according to the dimensional view, depression, and mental disorders in general, lie along a continuum and there is no need to differentiate them among categories (Haslam, 2003). This project approaches depression as a dimensional phenomenon. We believe

that the application of system dynamics goes together with the dimensional view since the severity of depression in each individual will depend on his or her characteristics (biological and cognitive resources). Thus, from a system dynamics view, we assume that the presence or absence of bipolar states in individuals will be the result of the dynamics of feedback mechanism. Thus, if the individual presents a unipolar depression, it would represent that the reinforcing feedback mechanism are too strong, depleting cognitive and biological resources (for example neurotransmitters or solving capacity) that could activate the balancing mechanism in order to generate pleasant episodes.

Theories and approaches to depression

In order to organize the existing literature regarding the etiology (causality) of depression for future model building, two sections have been recognized. This differentiation has been done according to the type of variables that they will represent in the model generated in this project. A similar study differentiated three dimensions for analyzing the different structures involved in depression: cognitive, social and environmental and biological (Wittenborn et al. 2015). In our case we merge the cognitive dimension with the social and environmental, since we believe the abstraction (perception) of the social dimension can be understood as cognition, obtaining two dimensions: cognitive and biological. Thus, in the following sections the main theories regarding depression will be documented in those two categories. Once they are individually explained, they will be represented in small causal loop diagrams, which will be combined in one systemic causal loop diagram.

Cognitive dimension of depression

A variety of cognitive theories and approaches have been developed through time, each of them coming with recommendations on how to treat depression. In general, most cognitive theories share a common hypothesis: the ways in which individuals attend to, interpret and remember negative life events contribute to the probability of experiencing depression (Lakdawalla, et al. 2007). Among the range of theories explaining the etiology of depression, we have selected three theories that have provided overall support for cognition as a central role in depression: Becks's Theory, Hopelessness Theory and Response Styles Theory; and one theory that explain depression in a more feedback oriented manner: Conservation of Resources (COR) stress theory.

The concepts used by the authors of the mentioned theories are not always consistent in terms of wording, for instance, the terms negative expectation of the environment and negative interpretation of the world may refer to the same concept, however in this section, we have tried to use the scholars terms unless it is necessary for clarification purposes. Therefore, some variables have small wording differences. For modeling purposes, the variables will be combined and the most easy to understand terms will be used.

Beck's Theory. Maladaptive schemas.

Beck's cognitive theory of depression (1967) proposes that individuals create negative cognitive self-schemas from three perspectives: negative view of the self, negative interpretation of the world and negative view of the future (Lakdawalla, et al. 2007). Self-schemas are created in early phases of peoples' life, usually during childhood, and can be inactive for a long period of time. However, once they are activated by specific events (stressful conditions), individuals will start presenting depressive symptoms. Thus, stress stimuli will serve as a switch for activating depression. Another contribution that fits in the explanation of depression as a switch that activates after stressful conditions is the scar hypothesis for depression development proposed by Lewinsohn and colleagues (1991). According the scar hypothesis, individuals who suffered from depression leave certain depressive scars after the depression symptoms have ended, making them more vulnerable for future depression (Calvete, 2013)

Beck's work has been criticized for saying little about the origins of depressive self-schemas, except suggesting that they are developed during childhood in response to early losses or other negative events (Cole et al. 2014). This line has been followed by Young and others who elaborated on the variety of maladaptive schemas, proposing two domains: disconnection and rejection, and impaired autonomy (Calvete et al. 2013). The disconnection and rejection maladaptive schemas are a result of the individuals' deduction that the expectations for security, acceptance and respect will not be fulfilled in a predictable (desirable) way. On the other side, the impaired autonomy maladaptive schemas consist of expectations about oneself and the environment that interfere with one's perceived capacity to perform successfully. Another author that has explored the causes of the creation of self-schemas is Cole (2014), proposing a model (Competence based model of depression) in which it is stated that one's level of social acceptance and

scholastic competence (ability to do schoolwork) contribute to the development of depressive symptoms. According to Cole (2015) people construct these self-perceptions out of feedback from significant others, and it is a major developmental task of middle childhood; again another proof for the creation of self-schema during childhood

Hopelessness theory. Negative inferences.

The hopelessness theory proposed by Abrahamson and colleagues in 1978, (initially as helplessness) states that some individuals present more depressogenic inferential styles and when they are confronted with a negative life event, they are likely to develop symptoms of depression. The theory proposes three types of negative inferences that individuals can make after the occurrence of negative events: causal inferences (attribute negative events to internal global, and stable causes), inferred consequences (attribute negative events as having important negative consequences that will affect many areas of one's life) and inferences about the self (draw negative inferences about oneself after negative events). After a person creates these inferences, a hopelessness view is more likely to appear, making an individual more vulnerable to depression (Lakdawalla, et al. 2007). Specifically important for this approach is the stress generation hypothesis proposed by Hammen (1991) which states that depressed individuals may contribute to the generation of additional stress in their lives. According to this hypothesis, previous levels of depression predict increases in future levels of stressors and these in turn contribute to perpetuate depression in individuals.

Response styles theory.

The response styles theory (Nolen-Hoeksema in 1991), proposes that the ways in which individuals respond to depressive symptoms determines the intensity and duration of symptoms. According to this view, there are three main response styles in an individual: rumination, distraction and problem solving (Hamilton et al. 2013). Special attention is paid on rumination since it will increase accessibility and recall of negative events, leading to more negative interpretations of behavior and it will reduce the individual's willingness to engage in actions that provide positive reinforcement. In general, ruminators will find difficult to generate solutions to their problems, creating lower and poorer quality solutions. This view exposes that distractions and problem solving are used to counteract rumination. While problem solving is the attitude for trying to change unfavorable situations or to resolve problems, distraction involves engaging in

positively reinforcing activities to redirect one's attention from symptoms of distress and depression.

Special emphasis has been put to rumination as an important driver for depression in the contemporary research about depression. It has been studied (Weber and Exner, 2013) how the acceptance and belief of rumination as a good habit creates actual rumination in individuals generating appearance of depressive symptoms. Other authors have followed a similar line, analyzing the effect of rumination in perceived stress. For instance, Rimes and Watkins (2004) state that different types of ruminative behaviors have different consequences on negative self-judgments. Analytic and experimental self-focus are differentiated by the authors, concluding that analytic self-focus is statistically correlated to depressive mood while experimental self-focus is not. Now, in order to understand how individuals put in practice the three main behaviors (rumination, distraction and problem solving) proposed by the Response Styles Theory, the working memory concept must be identified. Working memory defined as the capacity system that provides temporary access to a select set of representations in the service of current cognitive process, has been recently studied, from the cognitive point of view (Joormann & Gotlib, 2008) to demonstrate how depressed individuals' working memory is specifically affected and how their memory shows deficit in updating new contents due to interferences from irrelevant negative material. Moreover, deficiency in working memory has been statistically demonstrated to be a predictor for bad cognitive performance in individuals (Ganguli et al. 2014).

Conservation of resources stress theory and other social approaches to depression

One of the concepts proposed to explain the generation of stress from a psychosocial perspective is the Conservation of Resources (COR) stress theory (Hobfoll & Jackson, 1991). According to this theory, individuals seek to acquire and maintain resources, including personal features (self-esteem), life conditions (marriage, financial security), objects (house, belongings) or energies (time, money). If individuals perceive that they are having "losses" within the resources they have built or there is threat to lose them, for instance, losing financial security (money) after a crisis, or being threatened to lose a relationship, individuals will perceive stress (Ünal Karagüven, 2009). Thus, in order to fight stress and recover the resources lost, they will develop coping strategies. However, persistent threats to valued resources ultimately culminate in burnout, having negative

repercussions in individuals' life (feeding back as stressors and producing higher losses in resources). Thus, depressed individuals create a hopeless perception of themselves producing social withdrawal, which diminishes the opportunities of experiencing positive affect within their social circles. Joiner and others (2005) have coined the feedback structure of individuals developing hopeless perspectives, as an “addendum to the hopelessness theory of depression”. Nevertheless, these authors also recognize “braking” mechanisms that some individuals apply in order to stop going further in depression levels. According to this point, once individuals start presenting social withdrawal there will be a specific point in time where loneliness will drive individuals to generate alternative healthier sources of social support, putting them on track to recover (Joiner et al. 2005). Another aspect within the analysis of social interactions in depressive individuals, which needs to be considered, is marital or couple relationships because of the importance of emotional support during depression (Davila et al., 2003). While depressive symptoms tend to deteriorate relationships and marital satisfaction, the importance of partner's emotional support to depressive persons acts as a braking mechanism to avoid depression to escalate.

Biological dimension of depression

The instability of biological structures during depression has not always been accepted. In fact, depression was considered just a failure of character or a weakness of will within the biomedical community until the last century (Jacobs, 2004). The recognition of depression as a disease has been a result of experimental evidence, where biological structures of diagnosed depressed individuals (diagnosed with psychological tests) have been compared with the ones of non-depressed ones. Moreover, even when research has not always been consistent, giving sometimes contradictory results regarding some anatomical measures, it is accepted that during depression various biological structures present failures and do not work as expected. Currently, there are some biological mechanisms during depression that the biomedical community agrees on, and others that have gained space during the last decades, or are, in the lack of complete understanding, less controversial (contradicted) in the literature (Zunszain et al. 2010). We believe that in order to represent the dynamics of depression over time in a realistic way, modeling the feedback mechanisms of structures such as hormones, proteins and neurotransmitters is vital to understand the mechanisms underlying depression and how treatments affect them. Therefore, in the following section hormones, proteins,

neurotransmitters and structures affected by them during depression will be analyzed in an aggregate level. For instance, when talking about proteins, the specific names of every protein subtype will not be mentioned (unless clarification is needed) but how the whole group interacts within other important structures of the organism during depression according to the contemporary knowledge. As it has been mentioned during this project, we expect the model to be understood not only by specialists but other stakeholders such as patients and in general commoners involved in mental disorders, therefore the biomedical terms will be translated into “accessible” terminology.

The role of hormones (glucocorticoids) regulation

One of the key discovered features of depression is the disturbance in the functionality of specific hormones through the so-called *HPA axis* formed by the hypothalamus (H), the pituitary gland (P) and the adrenal cortex (A) (Zunszain et al. 2010). When a person is confronted with a stressful stimulus, the HPA axis activity starts with the secretion of corticotrophin-releasing hormone (CRH) in a part of the brain called the hypothalamus. As a result, in the pituitary gland, also within the brain, CRH activates the secretion of adrenocorticotrophin hormone (ACTH). Finally, ACTH travels to the adrenal cortex, located above the kidneys, and activates the secretion of glucocorticoids (mainly cortisol), which makes the organism alert in order to handle stressful situations (Pariante & Lightman, 2008). In an exemplification, when a person is confronted with short episodes of stress such as a possible car accident, the HPA axis comes to action and the secretion of glucocorticoids increases providing focused attention and alertness through the activation of other neurobiological structures such as neurotransmitters (Zunszain et al. 2010). Once the brain perceives that the stressful situation has passed, the HPA axis regulates itself, stopping the amount of glucocorticoids secretion and by decreasing the secretion of ACTH (in the anterior pituitary) and the secretion of CRH (in the hypothalamus). Thus, the production is stopped to go back to the normal rates that the organism was producing (Pariante & Lightman, 2008). This feedback process is shown in Figure 9.

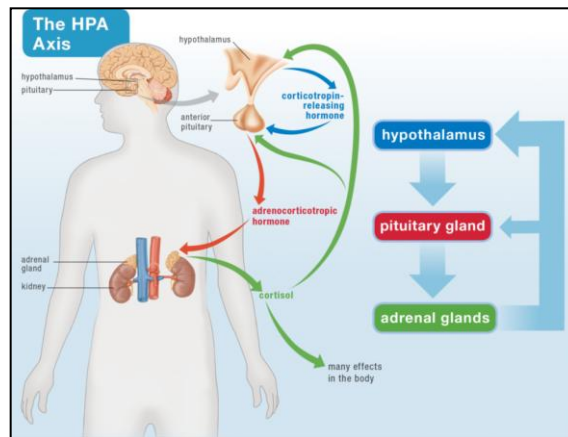


Figure 9. The HPA axis regulation process (taken from Ballantyne, 2013).

As mentioned before, over short periods of stress this mechanism alerts the organism to be ready for a possible threat, however when confronted with chronic stress exposure a malfunction occurs. The over-secretion of glucocorticoids during an extended period of time may create a negative effect in the HPA axis, generating impairment in the feedback process. This concept has been named as *glucocorticoids resistance*, and it is believed (it is uncertain) that the glucocorticoids receptor (GR), which is the structure responsible for regulating the HPA axis, would be the one suffering alterations and creating the malfunction (Zunszain et al. 2010). The presence of abnormal quantities of glucocorticoids in the blood and therefore in the brain will consequently cause other effects in the normal regulation processes within the organism, generating dangerous biological dynamics explained in the following sections.

Proteins and the inflammation process during depression

Another characteristic that has become more accepted over the years within the biomedical community is the presence of inflammation in depressed individuals (Miller et al. 2010). Patients with major depression, when compared to non-depressed individuals, present characteristics of inflammation in a similar way than the inflammation produced by physical injuries (Barros de Oliveira et al. 2011). It is believed that stress, as it would be a new wound, impulses the inflammatory processes, and the immune system (together with other cellular types) starts the production of pro-inflammatory proteins called cytokines. In order to counteract the pro-inflammatory proteins, the organism produces anti-inflammatory ones. One of the most important generators of anti-inflammatory proteins are hormones (glucocorticoids). Thus, the

production of hormones in the previously mentioned HPA axis helps to generate anti-inflammatory proteins that perform a process similar to the resolution of wounds in injuries (Barros de Oliveira et al. 2011). In general, the presence of short periods of stress does not disturb the organism since the auto-regulation of glucocorticoids will bring back equilibrium after the perception of the stress has ended (Pariante & Lightman, 2008). However, if there is glucocorticoids resistance (as a result of chronic stress exposure, the impairment of the glucocorticoids receptor would not be the only structure affected. Studies suggest that during chronic stress, the sensitivity of the inhibitory effect of glucocorticoids may be defective, meaning that even when there is a great amount of glucocorticoids that could generate the necessary amount of anti-inflammatory cytokines, they are not able to do it and inflammation would remain in the organism (overpopulation of pro-inflammatory cytokines) (Miller et al. 2010). As a result of the abundant quantity of pro-inflammatory cytokines in the blood, other structures and functions (sleep, physical condition, mood and others) will be affected and prolong the instability of the organism and the presence of depressive symptoms (Zunszain et al. 2010).

The role of neurotransmitters

Neurotransmitters are brain chemicals that communicate information throughout our brain and body (Liebmann & Weston, 2015). For instance, neurotransmitters are the structures telling the heart to beat, lungs to breathe, and for instance regulating cognition, motivation and intellect. Now, when certain neurotransmitters (specifically monoamines neurotransmitters) are out of balance, as it is the case during depression, they may cause a variety of complications in mood, sleep, weight, concentration and others. The biomedical community refers to this phenomenon as an alteration of the monoaminergic neurotransmission: an inadequate production of monoamines neurotransmitters (serotonin, norepinephrine, dopamine among others) (Moret & Briley, 2016). For instance, deficiency of serotonin is related to anxiety, obsessions and compulsions; reduced norepinephrine is related with low energy, decreased alertness and cognitive ability; and deficiency in dopamine is associated with problems with motivation and pleasure (Moret & Briley, 2016). Since our intention is to look at the mechanisms of depression from an aggregate level we will not include every type of monoamines neurotransmitter but the whole group will be analyzed. Now in order to understand the regulation of monoamines neurotransmitters two types of monoamines

neurotransmitters must be identified, they are, excitatory (for instance norepinephrine) and inhibitory (for instance serotonin). Excitatory neurotransmitters are the ones stimulating the brain, while inhibitory are the ones bringing balance to the brain (Wheat & Hassan, 2008). The presence of pro-inflammatory proteins in the brain will activate the generation of excitatory neurotransmitters, bringing more anxiety to the individual. Since excitatory and inhibitory neurotransmitters are assumed to be regulated in feedback processes between them, the brain will try to increase the amount of inhibitory neurotransmitters in order to bring calm and stop anxiety and panic sensations. Now, with the presence of chronic stress, since pro-inflammatory proteins are over concentrated in the brain, they affect the availability of both excitatory and inhibitory neurotransmitters. This occurs since pro-inflammatory proteins activates specific enzymes which are synthesized with neurotransmitters, becoming new chemical structures, reducing the available neurotransmitters in the brain and affecting the equilibrium between excitatory and inhibitory neurotransmitters. The new amount and ratio between the types of neurotransmitters finally drive biological changes to happen, impacting the individual behavior.

Sleep disorders in depression

One of most common problems during depression is insomnia or hyper-somnolence (Benca & Peterson, 2008). Co-relational models have seeing sleep disturbances as an effect (result), for instance concluding that depressed individuals present higher rates of sleep disorders; and as a cause, presenting that patients with insomnia are up to 10 times more likely to have depression (Benca & Peterson, 2008). We believe it is especially important to understand sleep alterations not only as a consequence of depression but specially a driver for perpetuating depression. An individual who is not able to rest the *right* amount of hours will drastically reduce him or her cognitive performance which causes even more problems to manifest (relationships quality erosion, work related issues, among others). In order to understand how dysfunctional sleep patterns can be diminished, their biological mechanisms are necessary to analyze. Currently, various neurobiological mechanisms are hypothesized (still uncertain) to be responsible for affecting sleep patterns in depressed patients (Benca & Peterson, 2008). Two of the most recurrent ones are the alteration of monoaminergic neurotransmission and the over activity of the HPA axis. Since we are considering the over activity of the HPA axis a

precursor of inflammation and neurotransmitters alteration, we will take only the effect of alteration monoaminergic neurotransmission as the effect for sleep hours impairment. Scholars have studied sleep cycles and they have found two different cycle processes within sleep time. It has been shown that during the beginning of sleep the production of pro-inflammatory proteins is high, therefore if a person wakes at that period, characteristics as fatigue, pain and similar are shown. A different process occurs once the body is preparing for waking up. There, more anti-inflammatory proteins are generated after the activation of the HPA axis, in order to counteract the pro-inflammatory response. Therefore with the presence of sleep disorders, those two mechanism do not work in the desired way, and individuals generally wake up presenting inflammation signs, perpetuating sleep disorder.

The alteration of processing and memory

Some of the symptoms regarding depression are strictly related to memory and processing: diminished ability to think, diminished ability to concentrate and difficulty for making decisions. Therefore, we believe that it is necessary to analyze what the underlying mechanisms that would affect memory are. Even though authors recognize the necessity for further research in long-term and short-term memory, through experimentation some concepts have been accepted. For instance, it has been proven how by intentionally alter the availability of a specific protein (tryptophan) in individuals, the reduction of the neurotransmitter serotonin is achieved consequently affecting the memory of individuals (Sambeth et al. 2009). As we explained in the neurotransmitters section, the alteration of one neurotransmitter group (for instance inhibitory neurotransmitters) would affect the alteration of the other neurotransmitters group (excitatory neurotransmitter). Therefore, the entire neurotransmitters adjustment mechanism would be impaired, avoiding the recuperation of the individual. Now, according to scholars another critical factor influencing the alteration of memory and processing is be sleep quality. Deficiencies in neurotransmitters do not allow to send the right information and sleep is impaired. As a consequence, since the individual is not able to sleep as he or she was accustomed to, the adjustment process for pro and anti-inflammatory proteins is not regulated in the optimal way (or at least to the way the individuals was used to before experiencing depression), and memory is likely to be impaired as well as cognitive performance.

Depression treatments

When dealing with depressive symptoms, individuals usually start using generic common beliefs about depression based on recommendations. Having a good diet, reducing stress sources, exercising and sleeping well are normally suggestions that individuals receive from their social circles. Since all those recommendations share positive mechanisms that help relieving depressive symptoms, some persons may overcome without professional help what could be a possible depression. However, if symptoms start absorbing the person, the seek for the *right treatment* starts. Two options are the most considered: therapy based on psychology and therapy based on pills. In our perspective, understanding the mechanisms behind those two approaches is crucial to understand the dynamics in depression development once treatments are included. Besides, we consider two other approaches. One of them is the increasingly popular mindfulness meditation and the other one is based on the common belief that physical activity improves symptoms of depression. In the following sections each treatment approach is explained from an aggregate level and represented in causal loop diagrams.

Psychotherapy. Cognitive behavioral therapy (CBT)

Even when medication is becoming more popular for treating depression, psychotherapy is still considered the best approach for the long-term since it helps the individual to deal with future stressors, decreasing the likelihood of possible relapses (Alexandersdóttir et al. 2009). According to the American Psychological Association, psychotherapy is a collaborative treatment based on the relationship between an individual and a psychologist, in which both try to identify and change the negative thought and behavior patterns that affect the individual is his (her) daily performance (APA, 2016). Among the different psychotherapy approaches currently offered, cognitive behavioral therapy (CBT) is the most used one (McGinn & Sanderson, 2001). With cognitive behavioral therapy, psychologists attempt, together with the patient, to identify and modify the dysfunctional beliefs that maintain negative symptoms (Perivoliotis & Cather, 2009). While different variations of the CBT can be recognized, they all share the same basic characteristics: encourage patients to treat their beliefs as hypothesis to be tested (Hollon, 1998). If those hypotheses can be rejected, the person can stop falling with the same trap. For instance, negative interpretations of social activities expressed with statements as “it will not be that much fun anyway” may drive

disengagement in leisure or social activities, which could generate more stressors due to isolation and decrease in interpersonal relationships quality (Perivoliotis & Cather, 2009). These associations between beliefs and behaviors are addressed with cognitive behavioral therapy.

Mindfulness meditation

In recent years, engaging in meditation has become a common recommendation for persons experimenting mental disorders (Srivastava, 2011). The attention has reached the research medical community and more studies regarding the effectiveness of meditation in patients with clinical conditions have been conducted (Kim et al. 2013). Among meditation techniques, mindfulness meditation is one of the approaches becoming increasingly popular as a complementary strategy for psychiatric conditions (Marchand, 2012). In general, mindfulness represents the concept of simply experiencing the present moment, without trying to change anything. Thus, it is expected that during mindfulness the person becomes more able to observe thoughts and emotions with some detachment. In other words, the person does not engage with negative thoughts but acknowledges that they can come and go without producing stress (Marchand, 2012). Now, since meditation refers to the engagement in contemplation or reflection, mindfulness meditation can be referred to the contemplation of a state of mind where the person becomes an impartial witness to his (her) own experience, accepting things as they are in the present moment (Marchand, 2012). When mindfulness meditation is applied to depression, the objective is the disengagement from self-perpetuating pattern of ruminative and negative thoughts that contribute to relapse. Instead mindfulness looks for *reperceiving* (Marchand, 2012). The reperceiving mechanism is defined as the fundamental shift in perspective so that one person has a experiential self-referential thinking in which the person can step back from his (her) own thoughts and emotion. While achieving this perspective the person stops engaging in a narrative self-referential thinking in which the person is constantly engaged with thoughts and try to stop them or change them (Marchand, 2012). This is precisely important during depression since it can be used as a mechanism to cut some reinforcing loops of depression.

Physical activity as a treatment approach

There is a common belief that exercise acts as a mood stabilizer, and it is usually recommended for depressed individuals. Studies have consistently associated regular physical activity with better mental health and less levels of depression (Ströhle, 2009). In fact, other than distracting a person from the source of stressors, exercising has biological mechanisms of action for good mental health. For instance, physical activity can help decreasing glucocorticoids (hormones), therefore avoiding impairments of proteins and neurotransmitters and all the negative consequences that overconcentration of glucocorticoids can bring. However, during depression patients and specialists should be aware of the intensity of physical activity, since it generates different results on circulating glucocorticoids in the blood (Hill et al. 2008). It has been proven that after exercising, circulating levels of glucocorticoids can either increase or decrease depending on the intensity of the exercise activity. This is precisely important during depression since it can be used as a mechanism (treatment) to reduce the overconcentration of glucocorticoids which have dangerous impacts in the rest of biological structures (effectiveness on anti-inflammatory proteins, sleep disorders, neurotransmitters impairments, among others) and consequently in cognitive performance

Pharmacological therapy (antidepressants pills)

Antidepressants medication (pharmacotherapy) is not precisely the first recommendation while a person starts presenting depressive symptoms. Actually, it is usually recommended that the first approaches to treat depressive symptoms should include cognitive therapy, exercise, or meditation, among others. However, authors expose that some depressive patients can be in state that does not allow them to engage in those activities, unless pharmacotherapy treatments are used to modulate neurotransmitters activity in the brain (for example Tucker, 2016). In order to correct these “biochemical imbalances” (the term used by physicians to communicate patients) various groups of antidepressants can be prescribed and even though it is often unclear why physicians prescribe a particular antidepressant (scientific grounds, pharmacoeconomic considerations, or marketing influence), the selective serotonin reuptake inhibitors (SSRIs) are the most prescribed antidepressants, due to the positive balance between efficacy and tolerability (Demyttenaere & Jaspers, 2008). SSRIs are intended to balance serotonin levels in the brain by regulating the activity or the quantity of serotonin, in order to improve the mood of individuals and all the benefits that it

produces (Woodruff, 2004). However, while attempting this and even though antidepressants have increased their tolerance within the years (for instance serotonin reuptake inhibitors show better results than the previous antidepressants), their side effects are still considerable (Demyttenaere & Jaspers, 2008). Bet and others (2013) documented the prevalence of twelve types of side effects during long-term treatments. From that list, we focus on four crucial side effects, since they could contribute to deeper levels of depression if not treated in an adequate manner. Those are: sleepiness during the day, weight gain and dizziness (for instance others are dry mouth, nausea, diarrhea, profuse sweating). These “crucial” side effects could be the drivers behind the correlation of antidepressants and psychological side effects, relationship that has been shown by different studies (Bitner et al. 2003).